REMARKS/ARGUMENTS

In response to the Office Action of August 9, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39, 40 and 44 have been amended. Claims 2-38 were cancelled in a previous response (filed on December 10, 2004). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to clearly indicate that the biopolymer marker consisting of SEQ ID NO:3 evidences a link to

Alzheimer's disease. This amendment is supported by the specification as originally filed; see page 35, lines 14-18, which discloses that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer markers which evidence a link to at least one specific disease state and page 46, lines 8-18, identifies SEQ ID NO:3 as a biopolymer related to the specific disease, Alzheimer's disease.

Claims 39 and 44 have been amended to remove the term "isolated".

Claim 40 has been amended to provide proper antecedent basis to the term "sample" in parent claim 39.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:3 a search of these claims would encompass this specific sequence. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the

decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker of SEQ ID NO:3 is found to be novel, methods and kits limited to its use should also be found novel.

Rejection under 35 USC 101

Claim 1, as presented on March 31, 2005, remains rejected under 35 USC 101 because the claimed invention is allegedly not supported by either a substantial, credible or a well-established utility.

The Examiner asserts that the disclosure does not clearly correlate sequences consisting of SEQ ID NO:3 with a link to Alzheimer's disease. Specifically, the Examiner asserts that the disclosure and the figures do not identify SEQ ID NO:3 and thus do not identify the differential expression of SEQ ID NO:3.

Applicants respectfully disagree with the Examiner's assertions.

Figure 3 is a photograph of a gel showing the results of a DEAE (anion exchanging) resin column chromatography protocol carried out to analyze a set of 9 samples; 4 serum samples obtained from patients with a history of Alzheimer's disease (lanes 1-4 as read from the left; AD-H-S-004, AD-H-S-005; AD-H-S-006 and AD-H-S-

008); 4 serum samples obtained from patients that are age matched with the Alzheimer's disease patients but do not have a history of Alzheimer's disease themselves (lanes 5-8, as read from the left, AG-AD-H-S-002, AG-AD-H-S-003, AG-AD-H-S-004 and AG-AD-H-S-005) and 1 serum sample obtained by pooling the serum sample of multiple patients who were all determined to be normal with regard to Alzheimer's disease (lane 9, as read from the left). Three bands are labeled; AG-AD-H-S-D3(E)C1, identified in a sample obtained from an age matched patient (lane 5), AD-H-S-D3(E)C2, identified in a sample obtained from an Alzheimer's disease patient (lane 1) and AG-AD-H-S-D3(E)C3, identified in a sample obtained from an age matched patient (lane 5).

According to the method of the invention, the criteria for evaluation is the identification of specific ions from the band on the gel and not the appearance of the band itself; i.e. bands are selected for further analysis based on differential expression observed in gels but peptides contained within the bands are ultimately identified by mass spectrometry, not by gel electrophoresis alone. A hypothetical example may serve to clarify. For example, a researcher has found that Band X is differentially expressed between a lung cancer patient and a patient who was determined to be healthy with regard to lung cancer. In hope of identifying potential markers for lung cancer, the researcher

subjects Band X to mass spectrometry and obtains three distinct mass spectral profiles. Two of these mass spectral profiles match to known proteins, Protein A and Protein B which the researcher then identifies as potential markers for lung cancer. The fact that multiple peptides were identified from one band does not diminish the value of the peptides as markers since it is the mass spectral profile which is unique and not the band itself. If a peptide is identified in a particular band, then it is present in the band regardless of the presence and/or absence of other peptides/proteins within the same band.

A mass spectral profile of peptides contained within Band 1 (AG-AD-H-S-D3(E)C1, as shown in Figure 3) is disclosed in Figure 5 of the instant specification. Figure 5 also discloses a chart listing ions obtained from Band 1 which were matched to peptides. This chart shows an ion having a molecular weight of 1873.9911 daltons which matched to (J02908) apolipoprotein J precursor (the claimed SEQ ID NO:3)and is associated with patients age matched to the Alzheimer's disease patients. Thus, Band AG-AD-H-S-D3(E)C1 corresponds with sequences consisting of SEQ ID NO:3, i.e. Band 1 is identified as containing the claimed SEQ ID NO:3. Furthermore, page 46, lines 8-18 of the instant specification, which discloses peptides found to be related to Alzheimer's disease, identifies the claimed SEQ ID NO:3 as marker (J02908) apolipoprotein J precursor

having a molecular weight of about 1873.9911 daltons.

Thus, contrary to the Examiner's assertion, the disclosure and the figures do identify the claimed SEQ ID NO:3.

Additionally, in Figure 3 it can be seen that Band 1(AG-AD-H-S-D3(E)C1, age matched to Alzheimer's disease) is expressed at a higher level than Band 2 (AD-H-S-D3(E)C2, Alzheimer's disease) at a corresponding molecular weight, indicating that increased levels of the peptides contained in Band 1, including the claimed SEQ ID NO:3, are found in patients age matched with the Alzheimer's disease patients. Thus, contrary to the Examiner's assertion, the figures and the disclosure do clearly identify the differential expression of SEQ ID NO:3 between Alzheimer's disease patients and patients age matched with the Alzheimer's disease patients.

In order to illustrate this point, Applicants herein provide the attached Declaration (and figure) under 37 CFR 1.132. The figure attached to the declaration is entitled "DEAE 3(Elution) AD vs. Age Matched AD (Control)" and represents Figure 3 as originally filed. This figure was produced by scanning the original photograph of the gel. No new matter has been added; this figure is simply a clearer copy of Figure 3 as originally filed and is provided to clarify the presence and differential expression of SEQ ID NO:3 (the claimed biopolymer marker). The gel shown in the figure does not represent new experimentation; the figure shows a clearer image

of the original gel made at the time that the experiments described in the instant specification were first carried out.

Applicants contend that the invention has "real-world" value. The Examiner asserts that this argument was not found persuasive because utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are not substantial utilities. Apparently, the Examiner believes that Applicants' asserted utility for the instant invention requires further research in order to be deemed "substantial".

If an invention is determined to have "real-world" value, one skilled in the art can use the claimed discovery in a manner that provides some immediate benefit to the public (as established in *Nelson v. Bowler and Crossley* 206 USPQ 881).

The instant invention provides a mass spectral profile of a peptide which was determined to be linked to Alzheimer's disease. This mass spectral profile can be used as a reference point for testing unknown samples for the presence of the peptide. Since the mass spectral profile is provided, no additional research is required to use the invention, (identifying the claimed SEQ ID NO:3 in a sample using the disclosed mass spectral profile).

Alzheimer's disease most often occurs in the elderly population. Advances in diagnosis and treatment of Alzheimer's

disease are highly desirable, especially since the elderly population is increasing. Thus, any advance in diagnosis and/or treatment of Alzheimer's disease would greatly benefit the elderly population which is susceptible to Alzheimer's disease. The claimed peptide (SEQ ID NO:3) represents an advance in Alzheimer's research; a "real-world" use benefitting the public, which satisfies the precedent set in *Nelson*. Thus, contrary to the Examiner's assertion, the instant invention has "real-world" value.

Furthermore, when considering practical utility ("real-world" utility) relevant evidence is judged as a whole for its persuasiveness in linking observed properties to suggested uses (*Nelson v. Bowler and Crossley* 206 USPQ 881).

The instant specification suggests that the claimed biopolymer marker (SEQ ID NO:3) is useful for diagnostics and/or therapeutics of Alzheimer's disease since it was found to be differentially expressed in Alzheimer's disease versus a normal physiological state (patients were age-matched to the Alzheimer's disease patients and were "normal" with respect to a history of Alzheimer's disease). Applicants respectfully assert that the observed differential expression is enough evidence such that one of ordinary skill in the art would be reasonably certain of the practical utility of the claimed biopolymer marker (SEQ ID NO:3).

Situations similar to the situation in the instant case have

occurred in the prior art wherein a marker was recognized to have practical utility based upon differences in expression in a disease state versus expression in a normal physiological state.

For example, Andreasen et al. disclose a study wherein the differences in concentration of β-amyloid (1-42 aa) in cerebrospinal fluid between early- and late-onset Alzheimer's disease was evaluated. Andreasen et al. found that levels of CSF-β-amyloid were decreased in patients with Alzheimer's disease compared with controls and from these findings suggested that CSF-β-amyloid analyses may be of value in the clinical diagnosis of Alzheimer's disease, especially in the early course of the disease, when drug therapy may have the greatest potential of being effective but clinical diagnosis is particularly difficult (see attached abstract of Andreasen et al. Archives of Neurology 56(6):673-680 1999; reference 1).

Since the data of Andreasen et al. was available in the art at the time of the invention, one of skill in the art would be familiar with such practice and thus likely to find that linking the observed differential expression of the claimed biopolymer marker (SEQ ID NO:3) to the suggested use of diagnostics and/or therapeutics of Alzheimer's disease is plausible.

Applicants further contend that the apolipoprotein J precursor is involved in Alzheimer's disease. Therefore, one of skill in the

art considering Alzheimer's disease would reasonably expect fragments of apolipoprotein J precursor such as sequences consisting of SEQ ID NO:3 to correlate to Alzheimer's disease. The Examiner asserts that this argument is not found to be persuasive because the specific sequences claimed were not previously taught in the prior art.

Applicants respectfully submit that the references cited in the prior response (Moulson et al. reference 2, Giannakopoulos et al. reference 3 and Zlokovic et al. reference 4) were not cited for the purpose of evidencing that the claimed SEQ ID NO:3 was taught in the prior art. Furthermore, Applicants respectfully contend that by requiring a showing of a direct link between the claimed SEQ ID NO:3 and Alzheimer's disease is requiring the Applicants to meet a standard higher than that which is necessary to satisfy the utility requirement under 35 USC 101, because it has been settled that an applicant is not required to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (MPEP 2164.07 I C).

Applicants respectfully submit that the references (Moulson et al. reference 2, Giannakopoulos et al. reference 3 and Zlokovic et

al. reference 4) were cited in the prior response as evidence to show that a person of ordinary skill in the art would be exposed to enough knowledge to conclude that the asserted utility for the claimed peptide (SEQ ID NO:3) is more likely than not true. Giannakopoulos et al. and Zlokovic teach that clusterin (ApoJ) has been associated with Alzheimer's disease. Zlokovic suggests that ApoJ exhibits an anti-amyloidogenic effect as it acts as a carrier protein of amyloid beta in body fluids, thus keeping it soluble. Amyloid beta which is soluble will not be deposited to form the plaques that are characteristic of Alzheimer's disease. Giannakopoulos et al. suggests that low cellular expression of clusterin (ApoJ) may be associated with the neuronal degeneration and death seen in Alzheimer's disease.

At page 46, lines 8-18 of the instant specification as originally filed, the claimed peptide (SEQ ID NO:3) is identified as a fragment of apolipoprotein J precursor protein. When one of ordinary skill in the art observes that the claimed SEQ ID NO:3, i.e. apolipoprotein J precursor protein, is differentially expressed in Alzheimer's disease patients vs. age matched patients, they would first want to know whether there is any known connection between Alzheimer's disease and apolipoprotien J precursor protein. Thus, one of ordinary skill in the art would be likely to come upon the cited references in a search for an answer to this question.

After reviewing the teachings of Moulson et al., Giannakopoulos et al. and Zlokovic one of ordinary skill in the art would find that ApoJ has been associated with Alzheimer's disease, and furthermore, a lack of ApoJ has been associated with the neuronal degeneration found in Alzheimer's disease. This data is in agreement with Applicants' finding of decreased expression of the ApoJ peptide in Alzheimer's disease patients. Accordingly, it is reasonable for one of ordinary skill in the art to believe that the claimed SEQ ID NO:3, i.e. apolipoprotein J precursor protein, more likely than not is linked to Alzheimer's disease.

In conclusion, based upon all of the above arguments and attached declaration (with figure), Applicants respectfully submit that one of ordinary skill in the art would immediately appreciate why Applicants regard the claimed biopolymer marker (SEQ ID NO:3) as useful.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on March 31, 2005, remains rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the

claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

The Examiner applies many of the same arguments used to support the rejection of claim 1 under 35 USC 101 to support the instant rejection of claim 1 under 35 USC 112, first paragraph.

Additionally, the Examiner asserts that Applicants' arguments were carefully considered but not found persuasive because the specification must teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention (*In re Gardner* 166 USPQ 138).

The instant specification discloses that SEQ ID NO:3 was identified as linked to Alzheimer's disease by carrying out mass spectrometry. The mass spectral profile of SEQ ID NO:3, shown in Figure 5, is provided as a reference which can be used by those of ordinary skill in the art to identify the presence of SEQ ID NO:3 in unknown samples. Thus, Applicants respectfully submit that the instant specification meets the requirements under 35 USC 112, first paragraph by teaching how to make and use the invention.

The Examiner asserts that the prior art teaches that Alzheimer's disease has no known cure, no known cause or mechanism, and cannot be definitely assigned as a differential diagnosis in

the absence of post-mortem examination and cites a reference, Patel, (Journal of Geriatric Psychiatry and Neurology 8:81-95 1995) which allegedly supports this view.

Apparently, the Examiner has dismissed the claimed biopolymer marker (SEQ ID NO:3) as "useless" based upon what Patel is deemed to teach.

The Examiner is reminded that the purpose of the patent system is to promote the progress of science and the useful arts (see "Introduction" of the MPEP and Article 1, section 8 of the US Constitution). Applicants respectfully submit that dismissal of an invention as "useless" simply because it has never been done before does not promote the progress of science and may discourage further medical research.

Patel presents an overview of the experimental drug therapy of cognitive impairment in Alzheimer's disease as the field was in the early 1990's. In contrast with the Examiner's interpretation of Patel's teachings, Applicants contend that Patel does not teach that there is no valid means for diagnostics of Alzheimer's disease other than post-mortem examination. Patel states at page 82, at the top of the left column:

"Over the years, many sets of diagnostic criteria for the clinical diagnosis of AD have been developed and refined, with the result that the diagnostic accuracy of AD has increased significantly. Today, the two most widely used clinical diagnostic criteria are those developed by NINCDS-ADRDA Work Group and the DSM III-R Work Group."

Thus, contrary to the Examiner's assertion, in the past ten years, many methods other than biopsy or post-mortem examination for diagnosing AD have been practiced and regarded as valuable; including Applicants' own patent, US 6,451,547 B1 (Jackowski et al.; reference 2) which claims methods for diagnosing Alzheimer's disease by detecting the presence of biochemical markers in bodily fluid.

The Examiner asserts that Applicant contends that the references of Tascilar et al. and Tockman et al. are not relevant to the instant invention because they do not teach SEQ ID NO:3 and its association to Alzheimer's disease. The Examiner then asserts that this argument is not found to be persuasive because the references were merely cited to show the state of the art with respect to marker discovery. A rejection is proper though a reference is not prior art when it establishes the level of ordinary skill in the art at the time of the claimed invention (see

Ex parte Erlich 22 USPQ 2d 1463).

Applicants respectfully submit that the Examiner has incorrectly interpreted Applicants' prior argument regarding the article of Tockman et al. since nowhere in the previous response (filed on March 31, 2005) do Applicants state that they believe the Tockman et al. reference is not relevant to the instant invention because it does not teach SEQ ID NO:3 and its association to Alzheimer's disease.

However, Applicants do not disagree that Tockman et al. establishes the level of ordinary skill in the art at the time of the claimed invention. As was discussed in the previous response (filed on March 31, 2005), Applicants assert that Tockman et al. link protein markers to disease in a manner analogous to that of the instant invention.

Tockman et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345) cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al.

link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer based upon expression. It does not appear that bombesin was "validated" and/or subjected to any "criteria" other than expression prior to this association. Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Thus, the teachings of Tockman et al. evidence that one of ordinary skill in the art would be inclined to link protein markers to disease prior to subjecting such markers to the extensive validation which the Examiner appears to be believe is a requirement for identification of potential biomarkers.

Accordingly, linking of the claimed SEQ ID NO:3 with Alzheimer's disease would not appear unreasonable to one of ordinary skill in the art since such linking practices were common

in the art at least as far back as 1992 (year of publication of Tockman et al.) well before the time of the instant invention.

In conclusion, Applicants claim that the differential expression of SEQ ID NO:3 between Alzheimer's disease patients and patients age matched to the Alzheimer's disease patients (determined to be normal with regard to Alzheimer's disease) evidences a link between the claimed peptide (SEQ ID NO:3) and Alzheimer's disease; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein in both the section under 35 USC 101 and the instant section. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (SEQ ID NO:3) and Alzheimer's disease and would further recognize how to use the claimed biopolymer (SEQ ID NO:3) as a marker for Alzheimer's disease. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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